Antibodies by Design:
Cracking the 'Undruggable' Code

The numbers that have long defined traditional drug discovery are, by any measure, daunting. Bringing a single new medicine to market can take over a decade and costs on average over $1billion. Despite this investment, only around 10% of drug candidates that enter clinical trials ever receive regulatory approval, and a smaller fraction of drug discovery programmes result in a marketable therapy.

These figures reflect not only economic inefficiency but also the limitations of existing discovery approaches in translating biological insight into effective therapeutics.

Conventional approaches rely heavily on high-throughput screening, which involves testing vast libraries of compounds against a target and hoping something binds. While effective for a subset of well-characterised and structurally accessible targets, this model is poorly suited to proteins that are dynamic, membrane-bound or insufficiently characterised. Up until recently, these have been referred to as "undruggable" targets, not impossible to drug in theory, but resistant to every conventional approach available in practice.

Recent advances in artificial intelligence (AI), particularly generative modelling, are beginning to address these limitations. Rather than screening existing chemical or antibody libraries, AI-enabled approaches allow for the design of novel molecules with properties optimised for specific biological targets.

This article will explore why traditional drug discovery has fallen short, what the emergence of AI-driven drug discovery has done to change the game and what the future holds for this new technology.

GPCRs as the Key

The term 'undruggable' has always been provisional, as it describes the limits of the methods available at a given moment. For G-protein coupled receptors (GPCRs), ion channels and other membrane-bound proteins, those limits have been especially pronounced.

GPCRs are among the most therapeutically important protein families, implicated in hundreds of diseases, spanning and accounting for approximately one-third of approved drugs, generating aggregate global sales approaching $1 trillion. Yet that extraordinary footprint covers only around 20% of the GPCR family. Estimates suggest that over two hundred GPCRs remain without targeted therapeutics, highlighting a substantial gap between biological understanding and therapeutic exploitation. The exceptional nature of these receptors has made traditional drug discovery very difficult.

The core challenge lies in membrane topology. GPCRs are embedded within the lipid bilayer, with the majority of their structure buried deep within the hydrophobic membrane environment. This leaves a limited extracellular surface area available for drug binding, and this surface must be engaged with considerable precision. Off-target binding, and the associated toxicity, is a considerable risk, leading to prolonged empirical screening campaigns with heavy reliance on chance.

Structural biology further complicates this landscape. Determining the crystal structure of a GPCR is technically demanding because extracting these receptors from the membrane causes them to lose their native conformation. Without reliable structural information, rational drug design is constrained, and discovery efforts revert to iterative screening. While antibodies offer increased specificity compared to small molecules, their application to membrane proteins introduces additional challenges, including the need for intact-cell screening systems and interference from co-expressed surface proteins.

Ion channels present similar barriers, including dynamic conformational states and conserved architectures that complicate selective targeting across subtypes. These characteristics collectively limit the effectiveness of traditional discovery approaches and contribute to the persistent gap in therapeutic coverage for these target classes.

Emergence of AI-driven Drug Design

AI-driven approaches are reshaping early-stage discovery by enabling the design of molecules based on learned representations of biological sequence, structure and function. Unlike traditional computational methods, which primarily rely on the analysis of existing libraries, modern generative models can propose entirely novel candidates optimised for defined target characteristics.

In antibody discovery, this shift is particularly significant as traditional antibody libraries are enormous and often largely random. In addition, for targets such as GPCRs, which adopt multiple distinct conformational states, AI models can be trained to design antibodies that preferentially bind specific functional states, thus introducing the possibility of achieving functional selectivity, rather than simply target engagement.

Once optimised candidates have been designed and developed, they are prioritised for experimental validation, creating a closed loop between computational prediction and wet-lab testing. The most effective AI-enabled approaches treat computational design not as a replacement for the wet lab but as a powerful upstream filter, dramatically compressing the hypothesis-to-candidate timeline by focusing experimental resources on molecules that models have already identified as high-probability candidates. The result is not a wholesale replacement of experimental biology, but a fundamental reordering of how discovery programmes are sequenced and resourced.

Practical Considerations and Limitations

Despite its potential, AI-enabled discovery introduces new challenges alongside its advantages. Biological complexity does not dissipate in the presence of a generative model, and not all difficult targets become tractable simply because an AI platform has been trained on related structural data. For many membrane proteins, available datasets remain limited, requiring models to extrapolate from related systems with varying degrees of reliability.

This is compounded by broader questions of data quality and accessibility. For rare or undercharacterised targets, public databases are often insufficient to support reliable predictive performance and proprietary datasets held by individual organisations therefore confer a meaningful advantage, but also raise questions about equitable access to both the tools and the resulting medicines.

In addition, regulatory frameworks are still catching up with the science. Both the FDA and EMA are actively developing guidance on the use of AI and machine learning in drug development, but standardised validation frameworks for AI-derived evidence remain a work-in-progress. Novel discovery approaches, however well validated internally, must still navigate established preclinical and clinical pathways, and sponsors will need to demonstrate to regulators not just that their candidates perform but that the process by which they were designed is robust and reproducible.

Taken together, these factors reinforce the theory that AI certainly improves the probability of success but does not guarantee it. The fundamental challenges associated with human biology and disease complexity remain, even as the tools used to interrogate them become more sophisticated.

Future Outlook

The continued evolution of AI in drug discovery, including but not limited to conventional antibody formats, but also other therapeutic modalities, such as nanobodies and cell therapies, is likely to be shaped by improvements in data integration and model fidelity. Multimodal approaches that combine structural, genomic, proteomic and functional data have the potential to better capture biological complexity, particularly for dynamic systems such as membrane proteins.

Within pharmaceutical R&D, AI is increasingly being integrated as a core component of discovery rather than an adjunct capability. Partnerships between specialised AI platforms and established pharmaceutical organisations are accelerating this trend, enabling access to both advanced computational methods and the experimental infrastructure required for validation and development.

As more AI-designed candidates progress through preclinical and clinical pipelines, the evidence base supporting these approaches will strengthen. This is likely to influence target selection strategies, particularly for proteins that have historically been deprioritised due to technical difficulty.

All in all, for the industry, this shift represents a move towards more efficient exploration of complex biology. For patients, it means so much more; it creates the potential for new life-changing therapies targeting mechanisms that have previously remained beyond reach.

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